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Eosinophilic Esophagitis: Impact of Latest Insights Into Pathophysiology on Therapeutic Strategies

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Key Words

Eosinophilic esophagitis · PPI-responsive esophageal eosinophilia · Eosinophils · Budesonide · Fluticasone propionate · Elimination diet · Dilation · Pathogenesis

Abstract

Eosinophilic esophagitis (EoE) has been defined as a 'chronic, immune/antigen-mediated, esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation'. A peak value of ≥15 eosinophils/high power field has been defined as histologic diagnostic cutoff. Other conditions associated with esophageal eosinophilia, such as gastro-esophageal reflux disease, PPI-responsive esophageal eosinophilia or Crohn's disease, need to be ruled out before EoE can be diagnosed. Males are affected more frequently than females and most of the patients have concomitant allergies. Currently, the EoE prevalence is about 1 of 2,000 inhabitants in Westernized countries. The first EoE patients were described only 2 decades ago. Despite this short period, considerable progress has been made regarding the understanding of the pathophysiology, natural history, assessment of disease activity and with respect to evaluating different therapeutic options. Untreated EoE can lead to esophageal remodeling with reduced compliance and stricture formation, which represents the main risk factor for food bolus impactions. The therapeutic options can be summarized with the 3 D's, which stand for drugs, diets and dilation. Of note, as of yet, there is no EoE-specific drug that has been approved by regulatory authorities. This is, among other reasons, related to the lack of validated outcome measurement instruments until recently. Swallowed topical steroids such as budesonide or fluticasone represent the standard of care for treating symptomatic pediatric and adult EoE patients with inflammatory activity. Several trials have already evaluated different biologic therapies, such as anti-interleukin-5 or anti-IgE. Further studies are on the way. As a non-pharmacologic alternative, different dietary regimens exist. Dilation can offer long-lasting symptomatic response in case of stricturing EoE but does not have any impact on the underlying inflammation. This review highlights the latest insights regarding pathophysiology and its impact regarding current and future therapeutic strategies.

Definition of EoE and Diagnosis

The first consecutive case series of patients suffering from eosinophilic esophagitis (EoE) were published in 1993 and 1994 by Attwood et al. [1] and Straumann et al. [2]. The authors reported on a series of patients characterized by dysphagia and dense esophageal eosinophilic infiltration. It lasted until 2007 when an international expert panel published the first guidelines on the diagnosis

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and therapy of EoE [3]. In the updated 2011 guidelines, EoE was defined by an international expert panel as 'a chronic, immune/antigen-mediated, esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation' [4]. This definition highlights the fact that there exists no single test to affirmatively diagnose EoE, but that the diagnosis relies rather on a combination of typical symptoms and characteristic histologic findings. Of note, several differential diagnoses associated with esophageal eosinophilia have to be excluded before EoE can be diagnosed (table 1). EoE patients are mostly males and a high prevalence of allergies against inhalative or food antigens is observed. Symptoms, mostly dysphagia, are typically present already for years before EoE diagnosis is established [5].

Table 1. Differential diagnosis of esophageal eosinophilia

Diseases associated with esophageal eosinophilia
EoE
GERD
PPI-responsive esophageal eosinophilia
Eosinophilic gastrointestinal diseases
Esophageal infections (e.g., fungal, viral, parasitic)
Crohn's disease
Celiac disease
Achalasia
Hypereosinophilic syndrome
Pemphigus
Vasculitis
Drug hypersensitivity
Connective tissue diseases
Graft vs. host disease

Epidemiology of EoE

Several recently published studies have documented that the incidence of EoE is approximately 1 case per 10,000 inhabitants per year [6, 7]. In Westernized countries, a steady increase in incidence of EoE has been observed over the past 2 decades [5, 6, 8–11]. It has been debated whether this observation reflects a true raise in incidence of EoE or whether it is, among other things, related to an enhanced awareness for EoE by gastroenterologists and pathologists. Two population-based studies from Switzerland, one in the German speaking and one in the French speaking part, have shown that indeed EoE incidence and cumulative prevalence increases much stronger than the rate of annual upper endoscopies that was performed during the observation period [5, 12]. This finding speaks in favor of an increase in incidence and prevalence that is beyond the one that could be explained only by enhanced awareness for EoE by gastroenterologists and pathologists.

EoE prevalence in 2009 in the German speaking part of Switzerland was reported to be 42.8 per 100,000 persons, corresponding to 1 EoE patient in 2,336 inhabitants. These prevalence data compare well with the data from Dellon et al. [13] who evaluated the EoE prevalence in the United States to be 56.7 per 100,000 persons. In summary, we are confronted with an increasing incidence and cumulative prevalence of EoE in Westernized countries.

Up to 80% of EoE patients have concomitant atopic diseases and the majority of them has allergies against food antigens and/or aeroallergens as defined by skin prick and/or allergen-specific IgE tests [14]. Allergen avoidance by dietary measures is successfully used in the treatment of EoE [15–17]. Based on findings from controlled food reintroduction, milk and wheat have been identified as the leading causative food categories [17].

Pathophysiology

The pathogenesis of EoE is still incompletely understood. It is generally accepted that it results from a complex interplay between genetic, environmental and host immune system factors. The esophagus is normally devoid of eosinophils; as such the finding of esophageal eosinophils denotes an underlying pathology, such as EoE or gastro-esophageal reflux disease (GERD) [18].

An overview of the pathogenesis is provided in figure 1. Several groups found esophageal barrier defects that might facilitate the entry of food allergens or swallowed aero-allergens. Rothenberg and colleagues focused on cadherins, a group of junctional proteins within the desmosomes, in particular, on the adhesion molecule desmoglein-1 (DSG1) [19]. They found that DSG1 is >20 times downregulated in active EoE compared to controls and that DSG1 deficiency leads to a structural alteration of the mucosa. Another group found that in children with active EoE, the expression of the intercellular junction proteins E-cadherin and claudin-1 is reduced [20]. Obviously, in active EoE, the mucosal integrity is altered due to defects in desmosomal and tight junction adhesion proteins. Interestingly, functional defects in desmosomes are reversed by successful treatment of EoE, and the func-

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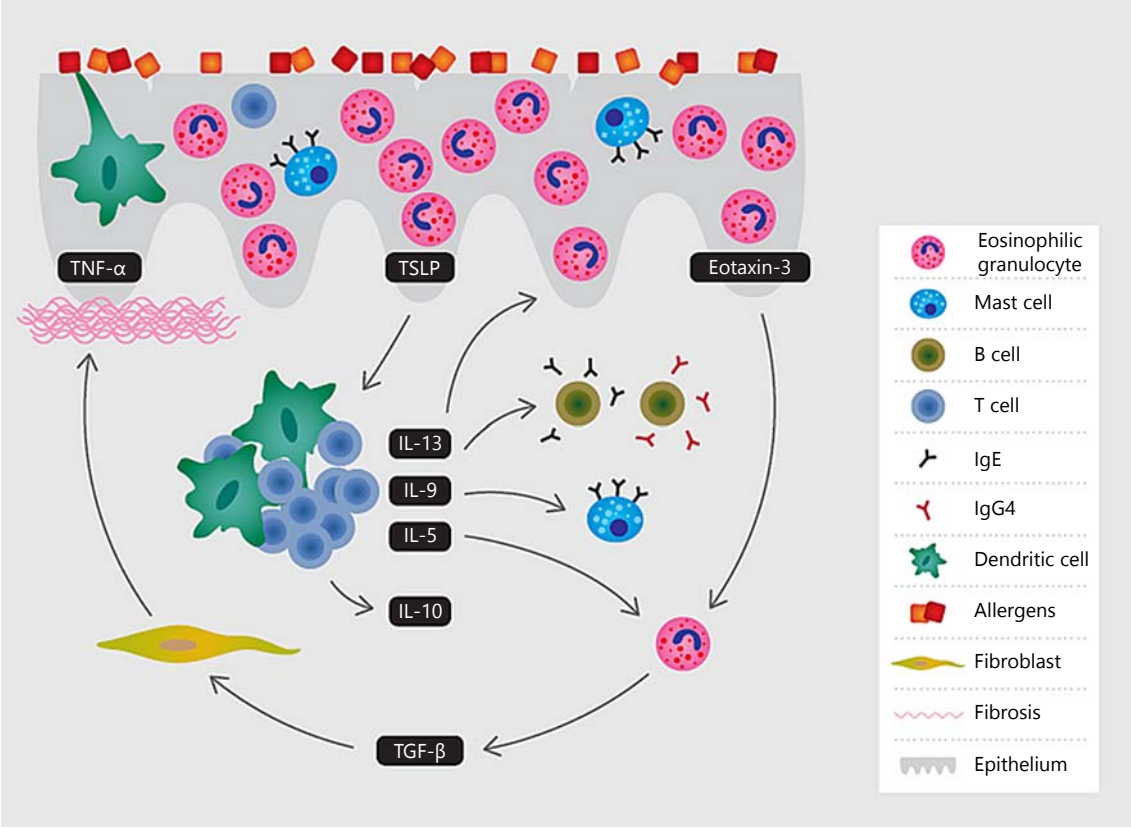

Fig. 1. Simplified immunopathogenesis of EoE. EoE is probably triggered by food allergens and aeroallergens. Epithelial barrier defects might facilitate the entry of allergens into the esophageal epithelium. Dendritic cells process allergens and produce, among other cytokines, TNF-alpha which increases adhesion molecules on endothelial cells. The esophageal epithelium produces TSLP that promotes dendritic-cell mediated Th2 differentiation. Eotaxin-3, which is expressed by the esophageal epithelium, attracts eosinophils. IL-13 promotes B-cells to produce IgE and IgG4. IL-9 activates mast cells that bind IgE. IL-5 promotes eosinophil maturation in the bone marrow and activates eosinophils. Eosinophils express TGF-beta which stimulates fibroblasts to produce extracellular matrix proteins.

tion of the mucosal barrier of patients having remittent EoE and of healthy controls is almost comparable [19]. These findings speak in favor of the fact that disturbed mucosal integrity in EoE is the result, and not the cause, of the chronic eosinophil inflammation.

Antigenic proteins, which are typically derived from food and less frequently from inhaled proteins, trigger an adaptive T helper 2 (Th2) cell-mediated response that produces a set of different cytokines, such as interleukin (IL)-5 and IL-13. IL-13 subsequently triggers esophageal resident cells such as the epithelial cells to produce a large set of proteins. Thymic stromal lymphopoietin (TSLP) promotes dendritic cell-mediated Th2 differentiation while tumor necrosis factor alpha (TNF-alpha) increases adhesion molecules on endothelial cells. The protein eotaxin-3 is strongly expressed by the esophageal epithelium and recruits eosinophils from the peripheral blood into the tissue [21]. Antigen-driven Th2 cells also produce IL-5, which activates eosinophils and enhances their responsiveness to eotaxin-3 and prolongs also their cellular survival. Eosinophils, T-cells and mast cells are elevated in esophageal mucosal biopsies with T-cells being polarized toward a Th2 immunity [22]. A recent publication highlighted a role for IgG4 in EoE pathogenesis [23]. The production of transforming growth factor beta (TGF-beta) by eosinophils leads to subepithelial fibrosis [24].

Natural History of EoE

Straumann et al. [5] were the first to address, in 2006, EoE's natural history by reporting on a prospective case series of 30 adult patients with a mean of a 7.2 years follow-up period. Patients were not under any anti-eosinophil

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treatment nor were they treated with elimination diets during their follow-up. Dysphagia as well as eosinophilic esophageal infiltrations persisted over time. In addition, authors noted the development of subepithelial fibrosis over time [5]. The first data on the natural history of pediatric EoE patients was published in 2007 and evaluated 89 pediatric EoE patients over an 8-year follow-up period [25]. EoE was found to be a chronic and relapsing condition, associated with atopy [25]. A retrospective study from Mayo Clinic Rochester among 32 adult EoE patients revealed that over a mean follow-up duration of 3.3 years, 91% of patients reported recurrent symptoms whereas 61% of patients repeated treatment with swallowed topical corticosteroids at least once [26]. A retrospective and prospective chart review of 620 EoE patients (whereof 330 patients had a follow-up period >1 year for analysis) at the Children's hospital of Philadelphia showed that EoE is a chronic disease and that <10% of patients developed tolerance to their food allergies [27]. A prospective study evaluating the role of epithelial mesenchymal transition (EMT) in 17 EoE patients, 15 patients with indeterminate EoE, 7 patients with GERD and 21 persons with normal esophagus showed that EMT likely contributed to subepithelial fibrosis in EoE patients and that it resolved under treatment that decreased esophageal inflammation [28]. Furthermore, the EMT resolution correlated with decreased numbers of esophageal eosinophils [28].

A retrospective study in 200 adult EoE patients from Switzerland found that with increasing duration of delay in diagnosis, the prevalence of fibrotic esophageal features increased from 46.5% (diagnostic delay 0–2 years) to 87.5% (diagnostic delay, >20 years) [29]. Similarly, the prevalence of esophageal strictures (defined as esophageal diameter of ≤10 mm) increased with duration of diagnostic delay, from 17.2% (diagnostic delay 0–2 years) to 70.8% (diagnostic delay, >20 years, $p < 0.001$). The length of diagnostic delay was identified as the only risk factor for strictures at the time of EoE diagnosis [29]. The findings from the Swiss EoE cohort were recently corroborated by a retrospective study in 64 adult EoE patients from Tampa, Florida [30]. A significant difference in mean time of delayed diagnosis in patients with <10 mm esophageal diameter (14.8 years) was found when compared to patients with an esophageal diameter of ≥17 mm (5 years, $p = 0.006$). These findings are in line with the results of a retrospective study in 379 adult EoE patients from University of North Carolina, Chapel Hill, that aimed to evaluate the clinical features of EoE patients with predefined phenotypes and to determine predictors of these phenotypes [31]. For each 10-year increase in age an odds ratio for fibrostenosis of 2.1 was identified. These findings suggested that the natural history of EoE represents a progression from an inflammatory to a fibrostenotic phenotype [31]. The natural history of untreated EoE is not only characterized by morphologic alterations such as esophageal strictures and histologically subepithelial fibrosis, but also functional abnormalities of esophageal motility [32].

Therapeutic Options

The therapy options can be summarized as the 3 D's, which stands for drugs, diet and dilation.

For an in-depth review of therapy recommendations, we kindly refer to the ACG guidelines [33]. Dietary therapy is effective as first-line treatment to induce histologic and clinical response and/or remission of EoE in pediatric and adult patients [16, 33–34]. Dietary therapy is based on the fact that the majority of EoE patients has food allergies that might contribute to EoE pathogenesis. It offers the advantage of a non-pharmacologic treatment strategy and can be successfully used in the long-term run [35]. There exist 3 types of diets: an aminoacid-based formula diet, a targeted elimination diet (which is based on the results of skin testing and serum IgE levels) and the empiric elimination diet. In the empiric elimination diet, the most frequently offending food categories are avoided (milk, wheat, eggs, soy, seafood, nuts). The identification of the offending food(s) is performed based on selective re-introduction of foods with endoscopic and histologic control [33].

The following pharmacologic treatment options exist for EoE: acid suppression, swallowed topical glucocorticoids such as budesonide, fluticasone propionate, ciclesonide and, rarely necessary, systemic steroids. In addition, several biologic therapies have been evaluated.

GERD may mimic EoE, it may coexist with it or contribute to it [36]. On the other hand, EoE can also contribute to GERD as it may impact the esophageal clearance [37]. EoE diagnosis is based on the persistence of esophageal eosinophilia despite a 2-month treatment with PPI or a normal pH-metric study [33]. EoE patients may profit from PPI therapy by reducing acid production in patients with coexistent GERD, or by PPI-inherent anti-eosinophil mechanisms [38]. PPI therapy may also be helpful in patients with established EoE as the altered esophagus may be predisposed and more sensitive to physiologic acid exposure [39]. About one-third of patients with clinical, endoscopic and histologic features

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compatible with EoE will show a clinical and histologic response to PPI treatment [33, 40]. These patients suffer from so-called 'PPI-responsive esophageal eosinophilia' and may be treated on a long-term basis by acid suppression [33].

As of yet, no anti-inflammatory drug has been approved by regulatory authorities specifically for EoE treatment. Swallowed topical budesonide and fluticasone propionate have consistently shown to effectively reduce esophageal eosinophil counts [41–44]. However, an improvement in dysphagia has not been consistently shown under swallowed topical steroids [41–44]. This observation might be related to the use of non-validated instruments for EoE symptom assessment or dietary modifications that might have resulted in a higher placebo response rate [45]. In fact, validated instruments to assess clinical EoE activity have become available only recently [46]. One trial with 4 children evaluated ciclesonide, a topical glucocorticoid with less systemic absorption than fluticasone and showed that symptoms as well as eosinophil counts significantly decreased after 2 months of treatment [47].

Systemic steroids are rarely used in EoE given their side effect profile and the generally high efficacy of topical swallowed steroids. One randomized trial evaluated oral prednisolone with swallowed topical fluticasone [48]. At week 4, almost all patients, irrespective of the treatment group, were free of symptoms whereas histologic improvement was noted to be greater in the prednisone group. As expected, glucocorticoid side effects were more frequently observed in the prednisone group when compared to the fluticasone group [48].

Several other treatment options have been evaluated for EoE. The leukotriene inhibitor, montelukast, reduced symptoms in one study but had no effect on esophageal eosinophil counts [49]. In another study, montelukast was inefficient in maintaining steroid-induced clinical and histologic remission [50]. One case series with 3 patients documented a clinical and histologic response on azathioprine or 6-mercaptopurine in steroid-dependent EoE patients [51]. In addition, several trials evaluated biologic therapies with targeted molecules. In 3 adult patients with glucocorticoid-dependent EoE, infliximab was not effective at resolving symptoms or esophageal eosinophilia (fig. 1) [52]. Mepolizumab is a humanized monoclonal antibody against IL-5, which has a key role in the recruitment of eosinophils (fig. 1). A placebo-controlled trial found a reduction of esophageal eosinophils in mepolizumab-treated patients when compared to patients treated with placebo, however in clinical terms, there was no statistically significant improvement [53]. Another study that evaluated 3 different doses of mepolizumab in pediatric EoE patients found a significant decrease in esophageal eosinophil counts and improvement in endoscopic findings in all 3 groups [54]. However, symptoms did not improve. Reslizumab, an IL-5 neutralizing antibody, was tested in 226 children and adolescents with EoE (fig. 1) [55]. Patients treated with reslizumab experienced a significant reduction in esophageal eosinophil counts when compared to placebo. However, there was no significant difference to the placebo group with regard to the change of symptoms [55]. Omalizumab, an anti-IgE antibody (fig. 1), was used in 2 patients with multiple food allergies and EoE. Omalizumab treatment improved allergic symptoms, but not endoscopic or histologic features of EoE [56]. There is one study evaluating an oral prostaglandin D2 receptor antagonist (OC000459). In a randomized trial, 26 adult patients with steroid-dependent or steroid-refractory EoE were randomized to either receive OC000459 or placebo. At week 8, OC000459 but not placebo was associated with a significant reduction in esophageal eosinophil counts and an improvement in symptoms [57].

In case of stricturing disease, esophageal dilation either by through-the-scope balloons or by Savary bougies can lead to long-lasting symptom improvement [58]. A recently published meta-analysis evaluated the efficacy and safety of esophageal dilation of 9 studies that included 525 patients who underwent a total of 992 esophageal dilations [59]. A total of 3 perforations and 1 hemorrhage were noted. Six studies reported post-procedural chest pain in 2% of patients. Clinical improvement from dilation was noted in 75% of patients. As such, esophageal dilation can be regarded as a safe procedure with a low rate of serious complications (<1%). Furthermore, esophageal dilation can lead to symptom improvement in the majority of treated patients. One drawback is that esophageal dilation does not influence the underlying eosinophilic esophageal inflammation. Lipka et al. [60] recently reported on a cohort of 13 adult EoE patients with a mean follow-up of 13.6 years that were treated by PPI and esophageal dilation once every 2 years. Authors concluded that this strategy appeared to be a safe long-term treatment.

In summary, despite the fact that the first EoE patients have been described only a little >20 years ago, considerable progress has been made in evaluating different treatment options as well as in understanding the pathophysiology and the natural history. As of yet, there is no drug on the market to specifically treat EoE that has an approval from regulatory authorities. The current treat-

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ment options have some inherent limitations. As such, the concerted effort of different stakeholders will be necessary to continue the endeavor of providing our patients with much-needed therapies.

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Disclaimers

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